PHASE 3 SUMMARY OF MRID 00116595:

PILOT TERATOLOGY STUDY IN RABBITS

STUDY # 281016

FLUMETRALIN

SUPPLEMENTAL INFORMATION IN SUPPORT OF

GUIDELINE REFERENCE:

83-3(B) TERATOGENICITY - RABBIT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

5 OCTOBER 1990

ORIGINAL STUDY PREPARED BY:

SCIENCE APPLICATIONS, INC.

LA JOLLA, CALIFORNIA

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

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GOOD LABORATORY PRACTICE STATEMENT

Science Applications, Inc. is no longer conducting toxicology business. Therefore, a GLP statement cannot be obtained from a study director or laboratory management. The attached pages from the report on this study indicate that the study was conducted under FDA Good Laboratory Practice Regulations (21 CFR 58).

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR Part 160 (see above).

Submitter/Sponsor of Study: Merrill Tisdel

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

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SCIENCE APPLICATIONS, INC.

QUALITY ASSURANCE STUDY INSPECTION AND COMPLIANCE STATEMENT

STUDY TITLE: A Dose Range-Finding Teratology Study of CGA-41065 Technical in New Zealand White Rabbits

TESTING FACILITY:

Science Applications, Inc.
Division of Toxicology
476 Prospect Street
P.O. Box 1454
La Jolla, CA 92038

SPONSOR NAME AND ADDRESS:

Ciba-Geigy Corporation
Agricultural Division
P.O. Box 11422
410 Swing Road
Greensboro, NC 27409

SPONSOR STUDY NUMBER: 281016

PRINCIPAL INVESTIGATOR:

Stephen B. Harris, M.S.

QUALITY ASSURANCE STATEMENT:

The following statements address the Food and Drug Administration's Good Laboratory Practices (GLP) requirements (CFR Title 21, Chapter I, Part 58 Subpart B, Section 58.35 (b)(7)) for final report.

A. Inspection and Reporting Statement: This study was inspected according to the Quality Assurance Unit's Standard Operating Procedures on the following dates:

Dates of Inspection	Phase of Study	Date Inspection Findings Reported to Principal Invest.	Dates of Management Reports
June 10, 1981	Animal Receipt	June 11, 1981	July 20, 1981
June 16, 1981	Animal Identification, Randomization	June 17, 1981	July 20, 1981
June 17, 1981	Protocol Compliance Review	June 17, 1981	July 20, 1981
June 23, 1981	Breeding, PLH Administration	June 23, 1981	July 20, 1981
June 30, 1981	Test/Control Article Formulation	June 30, 1981	July 20, 1981
July 1, 1981	Dose Administration, Body Weights, AM Clinicals	July 1, 1981	July 20, 1981
July 13, 1981	PM Clinicals	July 14, 1981	July 20, 1981
July 20, 1981	Study Notebook Maintenance	July 21, 1981	August 31, 1981

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SCIENCE APPLICATIONS, INC.

QUALITY ASSURANCE STUDY INSPECTION AND COMPLIANCE STATEMENT
(continued)

Dates of Inspection	Phase of Study	Date Inspection Findings Reported to Principal Invest.	Dates of Management Reports
July 24, 1981	Cesarean Sections, External Fetal Examinations	July 24, 1981	August 31, 1981
November 23, 1981	Raw Data Review	Not Reported	
March 11-15, 1982	Raw Data and Draft Final Report Review	March 15, 1982	

B. Compliance Statement:

The study was conducted in compliance with Good Laboratory Practices regulations.

S K Keener

Sharon K. Keener
Quality Assurance Manager

August 23, 1982
Date

CGA/SAI 281016

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Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

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83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y — Technical form of the active ingredient tested.
2. NA — At least 20 pregnant animals/dose group for mice, rats or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3. Y — At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.* Y — At the low dose, no developmental toxicity is reported.
5. Y — Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.* Y/N — Analysis for test material stability, homogeneity and concentration in dosing medium
7. Y — Individual daily observations.
8. Y — Individual body weights.
9. NA — Individual food consumption.
10. Y — Necropsy on all animals
11. Y/N — Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. Y — All ovaries examined to determine number of corpora lutea.
13. Y — Individual litter weights and/or individual fetal weights per sex/litter.
14. Y — Individual fetus external examination.
15. NA — Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. NA — Individual fetus soft tissue examination.

Criteria marked with a * are supplemental and may not be required for every study.

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IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name: N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine

or

2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine

Common Name: Flumetralin

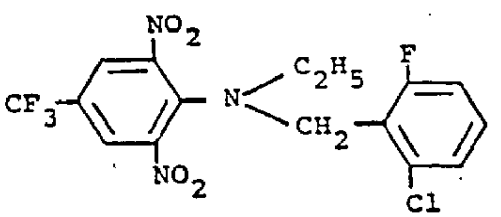
Trade Name: Prime +®

CIBA-GEIGY Code Number: CGA-41065

CAS Registry Number: 62924-70-3

EPA Shaughnessy Number: Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

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Flumetralin: 83-3(B): Pilot Teratology Study in the Rabbit

1. The test article was Flumetralin (CGA-41065) Technical, a bright orange crystalline substance, FL-810824, purity 92.7%.

2. There were six female New Zealand white rabbits in each of four test groups and a concurrent control. The dose levels were 0 (control), 100, 400, 800, and 1200 mg/kg of body weight per day of dosing.

3. There were 5, 2, 2, 1, and 2 viable litters in the control, 100, 400, 800, and 1200 mg/kg/day groups, respectively. Of four pregnant does in the 100 mg/kg/day group, two aborted. Of six pregnant does in the 400 mg/kg/day group, two aborted, one delivered early, and one died. Of four pregnant does in the 800 mg/kg/day group, one aborted, one delivered early, and one had no live or dead fetuses. Of five pregnant does in the 1200 mg/kg/day group, one aborted, one delivered early, and one died.

4. Signs of toxicity in the high-dose group included mortality (1/6), abortion (1/6), premature delivery (1/6), reduced absolute body weight gain (26% of control), increased numbers of resorptions, and decreased number of live fetuses.

5. The developmental no-observable-effect level in this study was 1200 mg/kg/day, the highest dose tested.

6. The animals were dosed by gavage for 13 consecutive days, from Day 6 through Day 18 of gestation (beginning June 28, 1981).

7. Test article/vehicle suspensions were prepared every three days. A sample from the first and last preparations of each dose level was retained and analyzed for concentration approximately five months after the preparations were mixed. Analytical concentrations averaged 114%, 92%, 76%, and 60% of target concentrations for the 100, 400, 800, and 1200 mg/kg dosing suspensions, respectively. Variation in concentration was attributed to difficulty in formulating the dosing suspensions. The dosing suspensions were not analyzed for homogeneity or stability.

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8. Does were observed daily for physical signs and/or general appearance. Discolored (yellow/orange) urine was observed in animals in all four test groups and was believed to be related to treatment with the test article. No other treatment-related observations were noted. Incidental observations included anorexia in the four test groups, ocular discharge, swollen conjunctiva, discharge in pan, and soft stool.

9. Body weights were recorded on Days 0, 6-18, 25, and 30 of presumed gestation. Small numbers of animals in each group precluded statistical analyses of body weights. However, average absolute body weight change from Day 6 to Day 30 averaged 95%, 78%, 9%, and 26% of control values for the 100, 400, 800, and 1200 mg/kg/day groups, respectively.

10. Food consumption was not measured in this study.

11. Does which died, aborted, or delivered early were not included in the analyses of the data. All other does were sacrificed on Day 30 of presumed gestation. The thoracic and abdominal cavities were opened and the reproductive organs were examined in situ. The uterus was excised and opened, and the location and distribution of live and dead fetuses and number and type of resorptions were recorded.

The most common necropsy findings in treated animals were yellow discoloration of the mesentery and yellow discoloration of the liver. The two animals which died on study were also found to have congestion or erosion of the stomach mucosa.

Parameter	Dose Level (mg/kg/day) 0	100	400	800	1200
Total Pregnant Does (N)	5	4	6	4	5
Delivered Early	0	0	1	1	1
Aborted	0	2	2	1	1
Found Dead	0	0	1	0	1
On-Schedule Laparohysterectomy	5	2	2	2	2
No Fetuses (live or dead)	0	0	0	1	0
Parameters for On-Schedule Laparohysterectomy Does					
Live Fetuses (mean/litter)	8.0	8.0	9.0	2.0	2.5
Live Fetuses (percent)	90.9	100.0	100.0	80.0	100.0
Resorbed Fetuses (mean/litter)	1.2	0.5	2.5	6.0	5.5

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12. Ovaries from all animals were examined to determine the number of corpora lutea. There were no differences among the groups in the number of corpora lutea, which averaged 9.8, 9.0, 11.0, 6.5, and 10.5 in the control, 100, 400, 800, and 1200 mg/kg/day groups, respectively.

13. Each apparently viable fetus in each litter was weighed individually. There were no differences among the groups in mean live fetal weights, which averaged 44.8, 55.8, 47.4, 46.0, and 47.0 g for the control, 100, 400, 800, and 1200 mg/kg/day groups, respectively.

14. Each fetus was examined for gross external abnormalities. One litter at 400 mg/kg/day had eight of nine fetuses with cleft palate, eight of nine with one or both eyes open, one fetus edematous and one with a hindpaw edema. One fetus at 1200 mg/kg/day had malrotation of digit #4 on both hindlimbs. No other external abnormalities were observed.

15. Because this study was a pilot study and was not intended to meet Guideline requirements, the Acceptance Criteria are not applicable. This study is summarized and submitted under Phase 3 to support dose selection in the definitive rabbit teratology study with Flumetralin Technical (MRID 00116596), which is also summarized in this Phase 3 submission.

GILLIS:R516SW0928JG/MT